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# Management of inherited thrombophilia in pregnancy

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## Abstract

Adverse pregnancy outcomes, such as pregnancy loss and pre-eclampsia, are associated with thrombotic mechanisms and thrombophilia. Antithrombotic interventions, particularly low-molecular-weight heparin, have been investigated in women identified by previous pregnancy outcome; however, the results have been inconsistent. This may reflect heterogeneity of both the study groups and the disease processes resulting in inadequate stratification to guide antithrombotic interventions. Furthermore, the variation in gestation at initiation of low-molecular-weight heparin treatment might be important. Despite limited evidence of efficacy, low-molecular-weight heparin is often used in an attempt to prevent these complications, owing to the lack of other effective treatments and its perceived safety in pregnancy. Research is required to better understand the disease processes, identify possible biomarkers and thereby more homogeneous groups for targeted treatment.

## Keywords

Inherited thrombophilia, pregnancy, low-molecular-weight heparin

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## Background

Pregnancy is a physiological prothrombotic state. Venous thromboembolism (VTE) is a leading cause of direct maternal death well described in the MBRRACE reports.<sup>1</sup> In addition, many adverse pregnancy outcomes, including fetal growth restriction (FGR), pregnancy loss, pre-eclampsia and placental abruption, which collectively affect up to 15% of pregnancies,<sup>2</sup> share similar and overlapping micro- and macro thrombotic pathogenic processes. The high physical and psychological burden of such adverse pregnancy outcomes makes the development of targeted and effective preventative interventions a significant issue for obstetric care. Despite limited evidence of benefit, the well-known association between thrombophilias and adverse pregnancy outcomes has led to widespread use of prophylactic low-molecular-weight heparin (LMWH) in pregnancy, as there are few interventions with biological plausibility for an effect.

## Physiological prothrombotic changes in pregnancy

Hypercoagulability is a physiological adaptation in pregnancy, reflecting a number of alterations in coagulation

and fibrinolytic pathways, which are summarised in Table 1. This hypercoagulant state increases through pregnancy, peaking at term.<sup>2,3</sup>

The endogenous anticoagulants, activated protein C (APC) and its vitamin K–dependent cofactor protein S, are reduced in pregnancy.<sup>4–6</sup> Fibrinolysis is reduced in pregnancy largely due to placenta-derived PAI-2; however, this normalises rapidly post-delivery.<sup>7</sup>

As pregnancy advances, tissue factor–dependent thrombin generation increases, along with Factors VII, VIII, IX, fibrinogen, prothrombin fragment 1+2 and

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**Table 1.** Haemostatic changes in pregnancy.

Anticoagulation/fibrinolysis	Procoagulation
Protein S ↓	Prothrombin (Factor II) ↑
Activated protein C ↓ in third trimester	Factor V ↑
Plasminogen activator inhibitor-I ↓	Factor VII ↑
	Factor VIII ↑
	Factor IX ↑
	Factor X ↑
	Fibrinogen ↑
	D-dimer ↑
	Systemic platelet activation ↑ in late pregnancy

thrombin-antithrombin complexes.<sup>8,9</sup> D-dimer levels increase through pregnancy reflecting the overall changes in coagulation and fibrinolysis in pregnancy.<sup>9</sup>

The placenta itself has procoagulant characteristics, with high levels of tissue factor expressed in trophoblast cells.<sup>10</sup> However, there are also inhibitory mechanisms such as endothelial protein C receptor, thrombomodulin, annexin V and tissue factor pathway inhibitor, which increases from the 10th week of pregnancy.<sup>7,11</sup>

## Inherited thrombophilias

The most common inherited thrombophilias are Factor V Leiden (FVL) and Factor II (prothrombin) G20210A, which affect 3–11% of the population; less prevalent (<1%) inherited thrombophilias include protein C, protein S and antithrombin deficiency, dysfibrinogenemias and hyperhomocysteinemia.<sup>12–14</sup>

### FVL

FVL accounts for 40–50% of inherited thrombophilias, with a prevalence of heterozygosity of 3–8% in the United States and Europe and as high as 8.8% in the white British population.<sup>15</sup> It is an autosomal dominant condition with incomplete penetrance, characterised by a relative resistance to active Protein C, leading to the inability of Protein C to cleave Factors Va and VIIIa because of a mutation at the cleavage site as a consequence of a single-nucleotide polymorphism. Its clinical expression varies depending on its homo- or heterozygosity and coexisting genetic and acquired disorders and risk factors.<sup>15</sup>

### Factor II (prothrombin) G20210A heterozygotes

The prothrombin G20210A polymorphism is a prevalent genetic variant in white populations with incidence of 1–6%. Factor II G20210A increases prothrombin and

thus greater thrombin generation and concurrently reduces APC-mediated inactivation of Factor Va.<sup>16</sup> This in turn leads to a prothrombotic state.

### Protein C deficiency

Protein C is a vitamin K–dependent natural anticoagulant, which inactivates Factors Va and VIIIa, thereby inhibiting thrombin generation.<sup>17</sup> Its deficiency can be a result of multiple different genetic mutations, leading to varying degrees of hypercoagulability.<sup>18</sup>

### Protein S deficiency

Protein S is a vitamin K–dependent cofactor of protein C, which only cleaves Factors Va and VIIIa in its free form.<sup>19</sup> Since Protein C anticoagulant activity is dependent on Protein S, deficiency in Protein S is associated with hypercoagulability. Protein S also has Protein C–independent roles, in which it directly inhibits factor Xase and prothrombinase and interacts with tissue factor pathway inhibitor to further inhibit factor Xa.<sup>20</sup> Its protein C–independent mechanisms are enhanced by LMWH.<sup>20</sup>

### Antithrombin deficiency

Antithrombin deficiency can be acquired and inherited; the inherited condition has a prevalence of 1 in 500–5000.<sup>21</sup> Antithrombin inactivates thrombin and Factor Xa; therefore, its deficiency promotes coagulation.<sup>21</sup> Quantitative Type I antithrombin deficiency results from heterozygous point mutations or major gene deletions leading to reduction in levels and function of antithrombin.<sup>22</sup> The more common qualitative Type II is associated with normal antithrombin levels and reduced function and is further categorised into IIa, b or c depending on which part of antithrombin is affected by the mutation.<sup>21</sup> Antithrombin functional assay is the initial investigation of choice, in order not to miss Type II deficiency. If abnormal, antithrombin antigen levels will distinguish between the two types. Functional assays assessing inhibitory activity on Xa have a higher sensitivity than those assessing thrombin and some patients with Type II antithrombin deficiency have only slightly reduced or even normal function, thus increasing the complexity of its diagnosis.<sup>21</sup>

### Dysfibrinogenemias

Congenital dysfibrinogenemias are rare and have an autosomal dominant pattern of inheritance.<sup>23</sup> They result in defects in the thrombin–fibrinogen reaction, preventing the conversion of soluble fibrinogen into insoluble fibrin. This in turn can lead to thrombosis, bleeding and defective wound healing.<sup>23</sup>

**Table 2.** Summary of associations between heritable thrombophilia and adverse pregnancy outcome.

	VTE	Early pregnancy loss	Recurrent first-trimester loss	Second-trimester loss	Late pregnancy loss	Pre-eclampsia	Placental abruption	FGR
Factor V Leiden	↑	↑	↑/↔	↑	↑	↑	↑	↔
Prothrombin G20210A	↑	↑	↑/↔	↑	↑	↑	↑	↔
Protein C deficiency	↑	↔	↔		↔	↑	↔	↔
Protein S deficiency	↑	↔	↔		↑	↔	↔	↔
Antithrombin deficiency	↑	↔	↔		↔		↔	↔
Hyperhomocysteinemia	↔	↔	↔		↔	↑	↔	↔

Data taken from Robertson et al.<sup>26</sup> and Rey et al.<sup>28</sup>

VTE: venous thromboembolism; FGR: fetal growth restriction.

### Hyperhomocysteinemia

Different inherited enzyme defects can lead to hyperhomocysteinemia. The most common is a single-nucleotide polymorphism in the methylene tetrahydrofolate reductase gene, MTHFR 677T. Homocysteine, when auto-oxidated, can lead to the production of biologically reactive products and increased cell toxicity. The four consequential disease processes include thrombosis, oxidant stress, apoptosis and cellular proliferation.<sup>24</sup> Folic acid, B12 and B6 supplements reduce circulating homocysteine levels; however, the clinical significance of this has yet to be demonstrated.<sup>25</sup>

### Thrombophilia and pregnancy

Data largely from retrospective cohorts and case control studies have shown that inherited thrombophilias are associated not only with VTE but also with adverse pregnancy outcomes including recurrent miscarriage and gestational vascular complications.<sup>26</sup> Initial reports such as that of Kupferminc et al.<sup>27</sup> reported as many as 65% of women with pre-eclampsia, unexpected stillbirth, placental abruption and FGR had some form of thrombophilia. More recent data, including from prospective studies, have demonstrated a more modest association. The evidence is summarised in Table 2. Inherited thrombophilias have also been linked to fertility problems and implantation failure, although no causal relationship has been proven.<sup>29</sup> As the overall effect of inherited thrombophilias on adverse pregnancy is modest, this suggests that their effect is likely to be contributory rather than a primary cause.

### Biological plausibility for thrombophilia and pregnancy complications

A satisfactory placental circulation is required for successful pregnancy development. Inadequate placental perfusion may reflect micro thrombotic events, which lead to a reduction in trophoblast invasion and chronic hypoxia.<sup>2</sup> This is thought to prompt gestational vascular complications including FGR, late pregnancy loss, placental

abruption and pre-eclampsia, which affect up to one in six pregnancies.<sup>30</sup> It is therefore logical to consider that prothrombotic conditions, including the inherited thrombophilias discussed in this review, could lead to an increased risk in such pregnancy complications. There are a number of examples, which demonstrate this biological plausibility in animal models.

The pathogenesis underlying the epidemiological and theoretical association between thrombophilias and adverse pregnancy outcomes has been studied. For example, Isermann et al.<sup>31</sup> studied mice with a disrupted gene coding for thrombomodulin. At the feto-maternal interface, thrombomodulin deficiency was associated with embryo abortion.<sup>31</sup> This study demonstrated the essential role of thrombomodulin in trophoblast growth and survival. At the feto-maternal interface, thrombomodulin deficiency stimulates a procoagulant cascade, thereby precipitating giant trophoblast cell death and arrest of growth of trophoblast cells.<sup>31</sup>

A report of mice with FVL highlighted the synergistic effect of both maternal and fetal thrombophilic mutations.<sup>32</sup> They found that FVL mice with fetal gene defects experienced fetal loss. This study also demonstrated that fetal loss was secondary to Par4-mediated platelet activation, interestingly in the absence of overt thrombosis. This has demonstrated the high-risk pregnancy model of concurrent fetal and maternal thrombophilia as well as a haemostatic pathogenesis independent of thrombosis.

The study by Jianzhong et al.<sup>33</sup> further complicated the role of thrombophilia and LMWH in recurrent pregnancy loss. The protective effect of LMWH on murine pregnancies was not reciprocated by fondaparinux, despite its comparable anticoagulant effect. This has highlighted a potential anticoagulant-independent effect of LMWH on placental development and the heterogeneity of placental-mediated complications.

### Early pregnancy loss

Heritable thrombophilias are associated with early pregnancy loss. A systematic review reported that

homozygotes for FVL and heterozygotes for FVL and prothrombin G20210A are at increased risk of early pregnancy loss (odds ratio (OR) 2.71 (95% confidence interval (CI) 1.32–5.58), 1.49 (95% CI 1.09–2.58) and 2.49 (95% CI 1.24–5.00)), respectively.<sup>26</sup> The other inherited thrombophilias showed no association with early pregnancy loss.

### ***Recurrent first-trimester loss***

There are modest associations between recurrent first-trimester loss and prothrombin G20210A heterozygosity, and with FVL (OR 2.70 (95% CI 1.37–1.69) and 1.91 (95% CI 1.01–3.61), respectively).<sup>26</sup> Such a weak association would again be consistent with thrombophilia being a contributory factor rather than a single cause of such complications.

### ***Second- and third-trimester pregnancy loss***

FVL and prothrombin G20210A heterozygotes have a stronger association with second-trimester loss than other early pregnancy loss (OR 4.12 (95% CI 1.93–8.81) and 8.60 (95% CI 0.44–1.69), respectively).<sup>26</sup> This was consistent with an earlier systematic review, which reported the strongest association to be between FVL and pregnancy loss after 19 weeks.<sup>28</sup> Rodger et al.'s<sup>34</sup> updated meta-analysis in 2014 looked at pregnancy loss irrespective of gestation and similarly found patients with FVL to be at increased risk (risk ratio 1.79 (95% CI 1.06–3.03)); it did not, however, find associations between prothrombin G20210A heterozygotes and overall pregnancy loss. Fewer studies exist for Protein C and S deficiency and poor pregnancy outcomes; however, Robertson's systematic review demonstrated a significant association between Protein S deficiency and late pregnancy loss although confidence intervals were wide reflecting small numbers (OR 20.1 (95% CI 3.70–109.15)).<sup>26</sup> There was no association with Protein C deficiency.

### ***Pre-eclampsia***

There is a modest association between FVL heterozygosity, prothrombin 20210A and MTHRR C677T homozygotes.<sup>26</sup> However, this was not confirmed in the systematic review of prospective studies.<sup>35</sup>

### ***Placental abruption***

Only two inherited thrombophilias have demonstrated statistically significant associations with risk of placental abruption; these are FVL heterozygotes and prothrombin G20210A heterozygotes.<sup>26</sup> Again, however, no association was found on meta-analysis of prospective studies.<sup>35</sup>

## ***FGR***

Although a generalised association between thrombophilia and FGR was demonstrated in a meta-analysis of five studies, meta-analyses of individual inherited thrombophilias demonstrated no significant association.<sup>32,35</sup>

## ***VTE***

VTE is a leading cause of direct maternal death<sup>1</sup> and thrombophilia is an established risk factor. For this reason, appropriate risk stratification and prophylaxis is crucial in women with thrombophilia in pregnancy. A systematic review demonstrated a relative increase in VTE risk in all inherited thrombophilias except homozygotes for MTHFR C677T; one explanatory hypothesis is that routinely taken folic acid supplements reduce homocysteine levels, thus reducing an increased VTE risk.<sup>26</sup> In contrast, the highest relative risk of VTE was associated with homozygous FVL (34.4%), translating to an absolute risk of 3.4%.<sup>26</sup> The more common thrombophilias demonstrated a weaker association. Early reports on the risk of VTE associated with deficiencies of antithrombin, Protein C and Protein S may have overestimated the risk due to methodologic limitations such as selection bias in family studies<sup>36,37</sup> as more recent estimates suggest a much lower level of risk.<sup>38</sup> A significant risk factor is family history of VTE, irrespective of thrombophilia; this increases risk twofold to fourfold.<sup>39</sup>

## ***Current guidance***

The lack of a strong and consistent evidence base to underpin clinical guidelines leads to differing recommendations in clinical guidelines such as from the American College of Chest Physicians (ACCP)<sup>38</sup> compared with the Royal College of Obstetricians and Gynaecologists (RCOG) guideline on thromboprophylaxis<sup>40</sup> (Tables 3 and 4).

Given the weaker association between the more common thrombophilias and VTE and the significant risk factor of positive family history, the ACCP guidance recommends LMWH prophylaxis in two groups of women: (1) with no family history of VTE who are either homozygotes of FVL or prothrombin gene mutations; or (2) women with family history of VTE in combination with any other inherited thrombophilia.<sup>38</sup> The ACCP guideline does not recommend prophylactic LMWH use for those with inherited thrombophilias in the absence of previous pregnancy complications. This is justified by the lack of the existing evidence for improvement in pregnancy outcome by LMWH in women with inherited thrombophilias and recurrent pregnancy loss.<sup>38</sup> However, the ACCP guideline does recommend aspirin for those who are at high risk of pre-eclampsia, irrespective of thrombophilia history. This is in-keeping with the American Congress of Obstetricians and Gynecologists (ACOG)<sup>41</sup> and supported by a strong evidence base.<sup>42</sup>

**Table 3.** Recommendations for thromboprophylaxis for women with inherited thrombophilia in pregnancy.

History of VTE	Inherited thrombophilia	Antenatal management	Postnatal management
Previous VTE	Antithrombin deficiency	50–100% treatment dose LMWH Involve haematologist Anti-Xa monitoring Consider prophylactic dose LMWH	50–100% treatment dose LMWH $\times$ 6 weeks/until oral (PO) anticoagulation started Prophylactic dose LMWH $\times$ 6 weeks
Asymptomatic	All others		
	Antithrombin deficiency		
	Protein C deficiency		
	Protein S deficiency		
	Compound heterozygotes		
	Homozygous FVL	If more than one thrombophilic defect, consider prophylactic dose LMWH	If more than one thrombophilic defect, for prophylactic dose LMWH $\times$ 6 weeks
	Homozygous prothrombin gene mutation		
	Heterozygous FVL	Consider prophylactic dose LMWH in the presence of three other risk factors/	Prophylactic dose LMWH $\times$ 10 days
	Heterozygous prothrombin gene mutation	from 28 weeks if two other risk factors	if one other risk factor

Data taken from RCOG Green-top guideline no. 37a.<sup>40</sup>

VTE: venous thromboembolism; LMWH: low-molecular-weight heparin; FVL: Factor V Leiden.

**Table 4.** ACCP guidelines for thromboprophylaxis for women with inherited thrombophilia in pregnancy.

History of VTE/pregnancy complication	Inherited thrombophilia	Antenatal management	Postnatal management
Previous VTE	Any inherited thrombophilia	Prophylactic or intermediate dose LMWH	Prophylactic or intermediate dose LMWH $\times$ 6 weeks
Asymptomatic but has family history of VTE	Homozygous for Factor V Leiden	Prophylactic or intermediate dose LMWH	Prophylactic or intermediate dose LMWH or vitamin K antagonists (INR 2–3) $\times$ 6 weeks
	Homozygous for prothrombin gene mutation	Prophylactic or intermediate dose LMWH	Prophylactic or intermediate dose LMWH or vitamin K antagonists (INR 2–3) $\times$ 6 weeks
	Protein C or S deficiency	Thromboprophylaxis <i>not</i> recommended	Prophylactic or intermediate dose LMWH $\times$ 6 weeks
	All other inherited thrombophilias	Thromboprophylaxis <i>not</i> recommended	Prophylactic or intermediate dose LMWH or vitamin K antagonists (INR 2–3) $\times$ 6 weeks
Asymptomatic and no family history of VTE	Any inherited thrombophilia	Thromboprophylaxis <i>not</i> recommended	Thromboprophylaxis <i>not</i> recommended
Previous pregnancy complications	Any inherited thrombophilia	Thromboprophylaxis <i>not</i> recommended	Thromboprophylaxis <i>not</i> recommended
High risk of pre-eclampsia	Irrespective of thrombophilia history	Low-dose aspirin from second trimester	Thromboprophylaxis <i>not</i> recommended

Data taken from Bates et al.<sup>38</sup>

ACCP: American College of Chest Physicians; VTE: venous thromboembolism; LMWH: low-molecular-weight heparin; INR: international normalised ratio.

The RCOG guidelines similarly recommend ‘consideration’ of antenatal LMWH prophylaxis in asymptomatic patients with homozygosity for FVL and prothrombin G20210A.<sup>40</sup> This guideline also recommends consideration of LMWH prophylaxis in women with antithrombin, Protein C or Protein S deficiency, despite the absence of family/personal history of VTE,<sup>40</sup> which differs from the ACCP guidance.<sup>38</sup> The RCOG guideline further stratifies risk by pragmatic accumulation of risk factors: if heterozygosity for FVL or prothrombin gene mutation is present

with two or three other risk factors, or there is compound heterozygosity, prophylactic LMWH can be given antenatally. Another difference between the two guidelines is that the RCOG guideline<sup>40</sup> applies risk stratification to dosing differences, suggesting that women with antithrombin deficiency and previous VTE should have 50–100% treatment dose antenatally and for 6 weeks postnatally.

ACCP and RCOG are just two examples of internationally available guidelines. The variation between these two guidelines alone exemplifies the lack of an adequate evidence base.

**Table 5.** The safety of LMWH in pregnancy.

Complication	Greer and Nelson-Piercy <sup>43</sup> Systematic review Rate % (n = 2777)	Nelson-Piercy et al. <sup>44</sup> Retrospective study Rate % (n = 1267)
VTE (overall)	0.86	1.19
VTE recurrence on treatment	1.15	1.97
Bleeding	Significant bleeding: 1.98 (1.50–2.57)	PPH > 500 = <1000 mL: 1.1 PPH > 1000 = <1500 mL: 0.9 PPH > 1500 mL: 1.1
Wound haematoma	0.61	0.9
Heparin-induced thrombocytopenia	0.00	0
Osteoporosis	0.04	0.2

LMWH: low-molecular-weight heparin; VTE: venous thromboembolism; PPH: postpartum haemorrhage.

## Discussion

There is an evidence base for management of VTE, in part, extrapolated from the non-pregnant population; however, the evidence base is limited for adverse pregnancy outcomes as discussed above. Due to the safety and relatively low side-effect profile of low-dose aspirin (LDA) and LMWH, as shown in Table 5,<sup>43,44</sup> the biological plausibility for an effect, extrapolation from Antiphospholipid syndrome (APS)<sup>45</sup> and the lack of alternative interventions, they have been introduced into care of groups at high risk of adverse pregnancy outcome in advance of evidence. Indeed, in three major randomised trials in women selected on the basis of previous pregnancy complications alone (rather than thrombophilia), such treatment was ineffective.<sup>46–48</sup> Interestingly, however, the trials from Gris et al.<sup>49,50</sup> on prevention of adverse pregnancy outcomes in women with a history of pre-eclampsia and abruption treated with LMWH showed significant benefit from LMWH. Of note, the women studied had a higher prevalence of thrombophilia (ca. 15%). In these randomised controlled trials, the pre-eclampsia rate was 5.8% with LMWH compared with 16.7% in the controls, and the incidence of severe pre-eclampsia was also significantly reduced in the LMWH cohort with a rate of 0.9% compared with 7.1%.<sup>49</sup> In women with a past history of abruption, the composite outcome of at least one of pre-eclampsia, placental abruption, birth weight under the fifth centile and fetal loss after 20 weeks was significantly lower in the LMWH group (12.5% compared with 31.3%).<sup>50</sup>

Furthermore, meta-analysis of six trials in this area is also consistent with some evidence of benefit from LMWH. In this meta-analysis, the study population was not specific to thrombophilia, but included pregnant women who had previous pregnancy complications including pre-eclampsia, placental abruption, small for gestational age (SGA) (<10th centile), second- and third-trimester pregnancy loss,<sup>51</sup> there was a significant reduction in the recurrence rate (18.7% in the LMWH group, versus 42.9% in the controls, relative

risk reduction, 0.52; 95% CI 0.32–0.86). They had similarly positive secondary outcomes with pre-eclampsia, SGA and preterm delivery. This demonstrates the potential for LMWH to be of value for women with previous placenta-mediated pregnancy complications, but requires corroboration with high-quality multicentre studies.

For women with a thrombophilia and history of adverse pregnancy outcome, this is an emotive area. Clinicians have no proven effective treatment, yet there is demand from patients for an intervention that might help. Clinicians are therefore obliged to actively manage such risk factors, despite the lack of good quality evidence supporting this. Although an increase in relative risk of VTE and adverse pregnancy outcomes has been demonstrated in the literature for those with inherited thrombophilias, the absolute risk is often low and the interventions are costly and do not come without risk. It is therefore important to consider the limited evidence behind these interventions.

For women with heritable thrombophilia, small non-randomised trials and observational studies have suggested some benefit.<sup>8</sup> However, this contrasts with data from recently reported randomised trials. The TIPPS trial studied women with thrombophilia and previous placenta-mediated pregnancy complications or VTE in a randomised trial of 146 women assigned to antepartum LMWH versus 143 assigned to no antepartum LMWH. There was a higher proportion of LDA use in the control group (40% versus 30%).<sup>52</sup> Given the fact that LDA has not previously been shown to be of benefit in such women, the difference in LDA use in the two groups should not affect the reliability of the data.<sup>45</sup> The trial demonstrated no significant reduction in adverse pregnancy outcome with LMWH treatment.<sup>52</sup> With regard to safety, major bleeding did not differ between the two groups, but minor bleeding was more common in the LMWH group (risk difference 10.4%, 95% CI 2.3–18.4;  $p=0.01$ ).

The FRUIT trial studied LMWH intervention in 139 women with inherited thrombophilia and a history of previous early-onset gestational hypertensive disorder.<sup>53</sup> In contrast to the TIPPS trial, it only recruited patients at less

than 12 weeks gestation and all patients received LDA. A significant reduction in hypertensive disease recurrence before 34 weeks gestation was demonstrated in women treated with LMWH and LDA compared with LDA alone, with a risk reduction of 8.7% (CI 1.9–15.5%;  $p=0.012$ ).<sup>53</sup> However, the overall hypertensive disease recurrence rate was unchanged with no difference in maternal or fetal outcome with no significant difference in gestation at delivery, only a reduction in antenatal steroid use in the LMWH group consequent upon the reduction in recurrence before 34 weeks of gestation.

Given the biological plausibility for a thrombotic mechanism and the potential for LMWH to impact on this, it is important to consider whether LMWH might still have a role in this disease process following the reports of the TIPPS and the FRUIT trials. There are data that show potential benefit from LMWH treatment on implantation and placental development including some data that suggest benefit on pregnancy outcome from LMWH in assisted conception treatment.<sup>28</sup> This leads to the hypothesis that the pathogenic processes originate in the first trimester. If this is the case, it is important to consider the timing of treatment in relation to implantation. In the TIPPS trial, less than 30% were recruited before 8 weeks' gestation.<sup>52</sup> This highlights the need to examine LMWH administration in the peri-implantation period.

Furthermore, similarities between the different placenta-mediated complications, including deficient implantation and placental infarction, have led to the theory that they share the same haemostatic pathological processes<sup>8</sup> and would therefore benefit from the same intervention. Perhaps this is naive as different disease mechanisms may be operating. Due to the complex multifactorial aetiologies of such outcomes and the heterogeneity of women studied in previous trials, it is possible that more convincing evidence for successful intervention may unfold if further research is targeted better through a disease process-specific approach.<sup>8</sup> This highlights the need for further research into the underlying disease mechanisms to allow better patient stratification, with a precision medicine approach allowing clinical trials to target more homogeneous populations with a disease process amenable to an antithrombotic intervention.

Such trials are not easy as evidenced by the TIPPS trial, which took 12 years to complete with centres in several countries.<sup>51</sup> Therefore, to recruit sufficient numbers of women with well-characterised disease mechanisms for a precision medicine trial will likely require a multi-centre international collaboration. Such an approach with a more homogeneous patient group is underway with the ALIFE 2 trial, which is randomising pregnant women of less than 7 weeks' gestation and confirmed inherited thrombophilia with a history of two or more miscarriages or intra-uterine fetal deaths, or both to LMWH plus standard pregnancy surveillance versus standard pregnancy surveillance alone ([www.ALIFE2study.org](http://www.ALIFE2study.org)).

## Conclusion

The widespread use of prophylactic anticoagulant and antiplatelet therapy for women with thrombophilia and a history of adverse pregnancy outcome based on the logical association between thrombotic processes and these complications has overridden the paucity of data supporting this treatment. Despite some studies demonstrating potential benefit of LMWH in women with previous placenta-mediated complications, there is as yet no good quality evidence supporting its antenatal use in those with inherited thrombophilia.

This lack of evidence may reflect the multifactorial nature of these complications, heterogeneity of the study groups with inadequate stratification or the variation in gestation at which LMWH has been introduced in these studies. Acquiring such evidence is not easy. The TIPPS trial clearly demonstrates the difficult and lengthy process. In the meantime, clinicians and patients will need guidance on the management of these conditions based on the current evidence including the need to continue to pursue clinical trials in this area. Only with research to provide a better understanding of the disease processes, identification of possible biomarkers and better-targeted treatment can we guide clinical decision making in this important and emotive area.

## Future perspective

In 5 years, precision medicine, which is already widely used in cancer care, will hopefully have been introduced into obstetrics. With progressing research into the pathophysiology of adverse pregnancy outcomes and potential biomarkers, we should have sufficient knowledge for categorisation and risk stratification of adverse pregnancy outcomes by their disease process rather than their clinical outcome. Randomised trials of interventions targeted on specific disease processes will accumulate to create a sounder evidence base to better inform management in this complex area.

## Executive summary

- Pregnancy is a physiological prothrombotic state.
- VTE is a leading cause of direct maternal death.
- Adverse pregnancy outcomes, including FGR, pregnancy loss, pre-eclampsia and placental abruption, share similar micro- or macro thrombotic pathogenic processes.
- Heritable thrombophilia is associated with both gestational VTE and adverse pregnancy outcomes.
- The association between heritable thrombophilia and poor pregnancy outcomes has led to widespread use of prophylactic LMWH based on the safety of LMWH, biological plausibility for benefit and lack of alternative interventions.



- Trials of intervention with LMWH for adverse pregnancy outcomes show inconsistent results with no overall evidence of a major benefit, including women with both heritable thrombophilia and a history of previous adverse pregnancy outcome.
- The inconsistent evidence base may reflect the multifactorial nature of these complications and heterogeneity of the study groups with inadequate stratification, or the variation in gestation at which LMWH has been introduced in these studies.
- Research is required to provide a better understanding of the disease processes, identify possible biomarkers to guide treatment and examine the possible benefits of better-targeted antithrombotic treatment.

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